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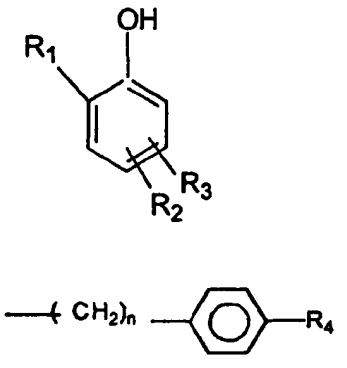
(54) Title: METHOD AND COMPOSITION



(57) Abstract: A method for inhibiting drug resistant bacteria which comprises administering to a host or surface in need of said treatment a composition comprising an antibacterially effective amount against drug resistant bacteria of a compound or a mixture of compounds of formula (I) wherein R_1 is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms; R_2 is at the 4 or 5 position and is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetrea alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms; wherein n is 0 or 1 and R_4 is selected from the group consisting of hydrogen, alkyl of one to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms; R_3 is selected from the group consisting of hydrogen and alkyl of one to three carbon atoms with the proviso that when R_2 is at the 4 position then R_3 is the 5 position and when R_2 is at the 5 position then R_3 is at the 4 position; and pharmaceutically acceptable salts thereof.

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METHOD AND COMPOSITION

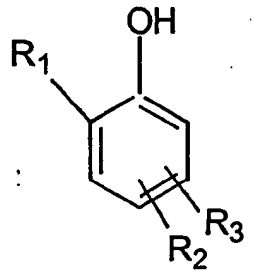
Field of the Invention

The indication and inhibition of disease causing bacteria has been one of the most significant events of the twentieth century. Diseases such as tuberculosis, pneumonia, and typhoid which were primary killers of people in the early twentieth century are presently far less significant diseases than they once were. One of the chief reasons for this phenomenon is the successful treatment of bacteria induced illness through the use of antimicrobial drugs such as antibiotics, semi synthetic antibiotics, and chemically synthesized compounds. However, bacteria have developed varying degrees of resistance to some or virtually all of these drugs. These "superbugs" can bring about a disease in a human which can result in death. Although such drug resistant bacteria can be found almost anywhere, they are a particular problem in hospitals, a locus where antibacterial drugs are used in high frequency. It has been recently reported that about 2 million hospital patients per year become infected, resulting in about 60,000 to 80,000 deaths. Staphylococcus bacteria, particularly staphaureus are the leading cause of hospital borne infection. Health care professionals are increasingly concerned about this issue. Greater focus is on the discovery of new chemical entities which will be successful in combating such bacteria.

It has now been discovered that certain types of compounds known to be effective antibacterial materials for many years are also effective against drug resistant bacteria. These compounds, particularly alkyl phenols, are effective against antibiotic resistant staphylococcus aureas (S. aureas). Specifically, these alkyl phenols are highly effective against methicillin resistant S. aureas.

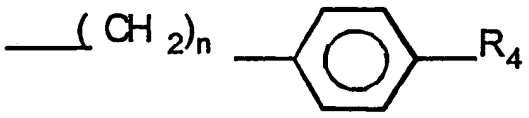
Summary of the Invention

In accordance with the invention, there is a method for inhibiting drug resistant bacteria which comprises administering to a host or surface in need of said treatment a composition comprising an antibacterially effective amount against drug resistant bacteria of a compound or a mixture of compounds of the formula:



wherein R_1 is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;

R_2 is at the 4 or 5 position and is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;



wherein n is 0 or 1 and R_4 is selected from the group consisting of hydrogen, alkyl of one to about twenty carbon atoms, cycloalkyl of from four to

about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms.

R_3 is selected from the group consisting of hydrogen and alkyl of three to eight carbon atoms with the provisio that when R_2 is at the 4 position then R_3 is at the 5 position and when R_2 is at the 5 position then R_3 is at the 4 position; and pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

The compounds of this invention are active against bacteria, particularly bacteria which are resistant to drugs and more particularly are very active against methicillin resistance bacteria such as members of the staphylococcus family, for example staphylococcus aureus. The active compounds of the invention inhibits the growth of the bacteria (bacteriostatic) and/or kill the bacteria (bactericidal).

The active compounds can be used as a disinfectant or in any other antibacterial compositions for example wherein it is the sole antibacterial active material or used in a combination with any other antibacterial compound wherein inhibition of bacteria is desirable or compound which promotes antibacterial activity. Examples of such other antibacterial active(s) include triclosan, triclocarbons, p-chloro-m-xylenol, thymol, benzethonium chloride, an antibiotic, and the like. The active compound(s) can be combined with any nontoxic to the host or surface compatible carrier to bring about the desired effect(s). Examples of such carrier(s) are water, alcohol, oils, glycols, surfactants and combination(s) thereof. Situations in which the active compound(s) can be administered are to inanimate surfaces which are in need of cleansing such as surgical instruments, floor(s), wall(s), glass area, plastic ware and the like in homes and particularly in settings wherein bacterial contamination is an issue such as nursing homes, assisted care living facilities, hospitals, bathrooms, kitchens and the like. Non-inanimate surfaces such as skin, hair, oral cavity, teeth, mucous membranes and the like can be treated through topical administration of a composition containing appropriate quantities of the active compound(s) such as solids, liquids, gels, aerosols,

emulsions, suspensions, ointments, salves, lotions, creams, toothpaste, mouthrinse, mucoadhesive materials, and other delivery vehicles.

The antibacterial active compound(s) can be delivered systemically to mammals, particularly humans in any nontoxic pharmaceutically acceptable vehicle in a minimum effective dose or more to a pharmaceutically effective nontoxic or essentially nontoxic maximum. The compound(s) can be delivered orally, topically or parenterally. The active compounds are particularly useful for mammals who are in need of treatment for antibacterial compound resistant bacteria, more particularly methicillin resistant bacteria. Examples of pharmaceutical dosage unit forms include pills, capsules, tablets, teaspoons, tablespoons, droppers, syringes and the like.

The quantities of active compound(s) which can be employed in the composition can vary from about 0.01 wt% to about 5 wt% of the composition for antibacterial treatment on an inanimate surface, desirably about 0.1 to about 2 and more desirably about 0.25 to about 1.0. For topical treatment of mammalian surfaces the quantity of active compound(s) which can be employed is from about 0.01 to about 1.0, desirably about 0.03 to about 0.5 and more desirably about 1 to about 0.35.

A particularly desirable method of treating inanimate or mammalian surfaces is using antibacterial effective amounts of the compounds of this invention in conjunction with cleansing effective amounts of a surfactant, particularly an anionic surfactant. For treatment of mammalian surfaces, it is preferable to use levels of a surfactant(s) which are above those level(s) used in a composition used in the oral cavity such as a toothpaste, gel, gum, powder, mouth wash and the like.

There must be at least one surfactant present in the composition. The surfactant can be anionic, nonionic, amphoteric, or cationic, preferably anionic. Soap, a long chain alkyl or alkenyl, branched or normal carboxylic acid salt such as sodium, potassium, ammonium or substituted ammonium salt can be present in the composition as an example of an anionic surfactant. Exemplary of long chain alkyl or alkenyl are from about 8 to about 22 carbon atoms in length, specifically about 10 to about 20 carbon atoms in length, more specifically alkyl and most specifically normal, or normal with little branching. Small quantities of olefinic

bond(s) may be present in the predominantly alkyl sections, particularly if the source of the "alkyl" group is obtained from a natural product such as tallow, coconut oil and the like. Because of its potential harshness soap is not a preferred surfactant and can be omitted from the composition unless a soap-containing bar is employed or mildness increasing corrections are employed.

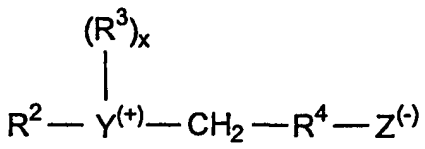
Other surfactants can be present in the composition in addition to or instead of soap. Examples of such surfactants are the anionic, amphoteric, nonionic and cationic surfactants. Examples of anionic surfactants include but are not limited to soaps, alkyl sulfates, anionic acyl sarcosinates, methyl acyl taurates, N-acyl glutamates, acyl isethionates, alkyl sulfosuccinates, alkyl phosphate esters, ethoxylated alkyl phosphate esters, trideceth sulfates, protein condensates, mixtures of ethoxylated alkyl sulfates and the like.

Alkyl chains for these surfactants are C_8-C_{22}, preferably C_{10}-C_{18}, more preferably C_{12}-C_{14}.

Anionic non-soap surfactants can be exemplified by the alkali metal salts of organic sulfate having in their molecular structure an alkyl radical containing from about 8 to about 22 carbon atoms and a sulfonic acid or sulfuric acid ester radical (included in the term alkyl is the alkyl portion of higher acyl radicals). Preferred are the sodium, ammonium, potassium or triethanolamine alkyl sulfates, especially those obtained by sulfating the higher alcohols (C_8-C_{18} carbon atoms), sodium coconut oil fatty acid monoglyceride sulfates and sulfonates; sodium or potassium salts of sulfuric acid esters of the reaction product of 1 mole of a higher fatty alcohol (e.g., tallow or coconut oil alcohols) and 1 to 12 moles of ethylene oxide; sodium or potassium salts of alkyl phenol ethylene oxide ether sulfate with 1 to 10 units of ethylene oxide per molecule and in which the alkyl radicals contain from 8 to 12 carbon atoms, sodium alkyl glyceryl ether sulfonates; the reaction product of fatty acids having from 10 to 22 carbon atoms esterified with isethionic acid and neutralized with sodium hydroxide; water soluble salts of condensation products of fatty acids with sarcosine; and others known in the art.

Zwitterionic surfactants can be exemplified by those which can be broadly described as derivatives of aliphatic quaternary ammonium, phosphonium, and sulfonium compounds, in which the aliphatic radicals can be straight chain or

branched and wherein one of the aliphatic substituents contains from about 8 to 18 carbon atoms and one contains an anionic water-solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. A general formula for these compounds is:



wherein R^2 contains an alkyl, alkenyl, or hydroxy alkyl radical of from about 8 to about 18 carbon atoms, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety; Y is selected from the group consisting of nitrogen, phosphorus, and sulfur atoms; R3 is an alkyl or monohydroxyalkyl group containing 1 to about 3 carbon atoms; X is 1 when Y is a sulfur atom and 2 when Y is a nitrogen or phosphorus atom, R^4 is an alkylene or hydroxyalkylene of from 0 to about 4 carbon atoms and Z is a radical selected from the group consisting of carboxylate, sulfonate, sulfate, phosphonate, and phosphate groups.

Examples include:

4-[N,N-di(2-hydroxyethyl)-N-octadecylammonio]-butane-1-carboxylate;

5-[S-3-hydroxypropyl-S-hexadecylsulfonio] -3 hydroxypentane-1-sulfate;

3-[P,P-P-diethyl-P 3,6,9 trioxatetradecyl- phosphonio]-2-hydroxypropane-1-phosphate;

3-[N,N-dipropyl-N-3 dodecoxy-2-hydroxypropylammonio]-propane-l-phosphonate;

3-(N,N-di- methyl-N-hexadecylammonio) propane-1-sulfonate;

3-(N,N-dimethyl-N-hexadecylammonio)-2-hydroxypropane-1-sulfonate;

4-(N,N-di(2-hydroxyethyl)-N-(2 hydroxydodecyl) ammonio]-butane-1-carboxylate;

3-[S-ethyl-S-(3-dodecoxy-2-hydroxypropyl)sulfonio]-propane-1-phosphate;

3-(P,P-dimethyl-P-dodecylphosphonio)-propane-1-phosphonate; and

5-[N,N-di(3-hydroxypropyl)-N-hexadecylammonio]-2-hydroxy-pentane-1-sulfate.

Examples of amphoteric surfactants which can be used in the compositions of the present invention are those which can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples of compounds falling within this definition are sodium 3-dodecylaminopropionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines, such as the one prepared by reacting dodecylamine with sodium isethionate according to the teaching of U.S. Patent No.2,658,072, N-higher alkyl aspartic acids, such as those produced according to the teaching of U.S. Patent No. 2,438,091, and the products sold under the trade name "Miranol" and described in U.S. Patent No. 2,528,378. Other amphoterics such as betaines are also useful in the present composition.

Examples of betaines useful herein include the high alkyl betaines such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxy-methyl betaine, lauryl dimethyl alpha-carboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, lauryl bis-(2-hydroxyethyl)carboxy methyl betaine, stearyl bis-(2-hydroxypropyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydro-xypropyl) alpha-carboxyethyl betaine, etc. The sulfobetaines may be represented by coco dimethyl sulfopropyl betaine, stearyl dimethyl sulfopropyl betaine, amido betaines, amidosulfobetaines, and the like.

Many cationic surfactants are known to the art. By way of example, the following may be mentioned:

stearyldimenthylbenzyl ammonium chloride;
dodecyltrimethylammonium chloride;
nonylbenzylethyldimethyl ammonium nitrate;
tetradecylpyridinium bromide;
laurylpyridinium chloride;
cetylpyridinium chloride
laurylpyridinium chloride;
laurylisoquinolium bromide;

ditallow(Hydrogenated)dimethyl ammonium chloride;
dilauryldimethyl ammonium chloride; and
stearalkonium chloride.

Additional cationic surfactants are disclosed in USP 4,303,543 see column 4, lines 58 and column 5, lines 1-42, incorporated herein by references. Also see CTFA Cosmetic Ingredient Dictionary, 4th Edition 1991, pages 509-514 for various long chain alkyl cationic surfactants; incorporated herein by references.

Nonionic surfactants can be broadly defined as compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound, which may be aliphatic or alkyl aromatic in nature. Examples of preferred classes of nonionic surfactants are:

1. The polyethylene oxide condensates of alkyl phenols, e.g., the condensation products of alkyl phenols having an alkyl group containing from about 6 to 12 carbon atoms in either a straight chain or branched chain configuration, with ethylene oxide, the said ethylene oxide being present in amounts equal to 10 to 60 moles of ethylene oxide per mole of alkyl phenol. The alkyl substituent in such compounds may be derived from polymerized propylene, diisobutylene, octane, or nonane, for example.

2. Those derived from the condensation of ethylene oxide with the product resulting from the reaction of propylene oxide and ethylene diamine products which may be varied in composition depending upon the balance between the hydrophobic and hydrophilic elements which is desired. For example, compounds containing from about 40% to about 80% polyoxyethylene by weight and having a molecular weight of from about 5,000 to about 11,000 resulting from the reaction of ethylene oxide groups with a hydrophobic base constituted of the reaction product of ethylene diamine and excess propylene oxide, said base having a molecular weight of the order of 2,500 to 3,000, are satisfactory.

3. The condensation product of aliphatic alcohols having from 8 to 18 carbon atoms, in either straight chain or branched chain configuration with ethylene oxide, e.g., a coconut alcohol ethylene oxide condensate having from 10 to 30 moles of ethylene oxide per mole of coconut alcohol, the coconut

alcohol fraction having from 10 to 14 carbon atoms. Other ethylene oxide condensation products are ethoxylated fatty acid esters of polyhydric alcohols (e.g., Tween 20-polyoxyethylene (20) sorbitan monolaurate).

4. Long chain tertiary amine oxides corresponding to the following general formula:

$$R_1R_2R_3N \rightarrow O$$

wherein R_1 contains an alkyl, alkenyl or monohydroxy alkyl radical of from about 8 to about 18 carbon atoms, from 0 to about 10 ethylene oxide moieties, and from 0 to 1 glyceryl moiety, and, R_2 and R_3 contain from 1 to about 3 carbon atoms and from 0 to about 1 hydroxy group, e.g., methyl, ethyl, propyl, hydroxy ethyl, or hydroxy propyl radicals. The arrow in the formula is a conventional representation of a semipolar bond. Examples of amine oxides suitable for use in this invention include dimethyldodecylamine oxide, oleyl-di(2-hydroxyethyl) amine oxide, dimethyloctylamine oxide, dimethyldecylamine oxide, dimethyltetradecylamine oxide, 3,6,9 trioxaheptadecyldiethylamine oxide, di(2-hydroxyethyl)-tetradecylamine oxide, 2-dodecoxyethyldimethylamine oxide, 3-dodecoxy-2-hydroxypropyldi(3-hydroxypropyl)amine oxide, dimethylhexadecyl-amine oxide.

5. Long chain tertiary phosphine oxides corresponding to the following general formula:

$$RR'R''P \rightarrow O$$

wherein R contains an alkyl, alkenyl or monohydroxyalkyl radical ranging from 8 to 20 carbon atoms in chain length, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety and R' and R" are each alkyl or monohydroxyalkyl groups containing from 1 to 3 carbon atoms. The arrow in the formula is a conventional representation of a semipolar bond. Examples of suitable phosphine oxides are: dodecyldimethylphosphine oxide, tetradecylmethylethylphosphine oxide, 3,6,9-trioxaoctadecyldimethylphosphine oxide, cetyldimethylphosphine oxide, 3-dodecoxy-2-hydroxypropyldi(2-hydroxyethyl) phosphine oxide stearyldimethylphosphine oxide, cetylethyl propylphosphine oxide, oleyldiethylphosphine oxide, dodecyldiethylphosphine oxide, tetradecyldiethylphosphine oxide, dodecyldipropylphosphine oxide,

dodecyldi(hydroxymethyl)phosphine oxide, dodecyldi(2-hydroxyethyl)phosphine oxide, tetradecylmethyl-2-hydroxypropylphosphine oxide, oleyldimethylphosphine oxide, 2-hydroxydodecyldimethylphosphine oxide.

6. Long chain dialkyl sulfoxides containing one short chain alkyl or hydroxy alkyl radical of 1 to about 3 carbon atoms (usually methyl) and one long hydrophobic chain which contain alkyl, alkenyl, hydroxy alkyl, or keto alkyl radicals containing from about 8 to about 20 carbon atoms, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety. Examples include: octadecyl methyl sulfoxide, 2-ketotridecyl methyl sulfoxide, 3,6,9-trioxaoctadecyl 2-hydroxyethyl sulfoxide, dodecyl methyl sulfoxide, oleyl 3-hydroxypropyl sulfoxide, tetradecyl methyl sulfoxide, 3 methoxytridecylmethyl sulfoxide, 3-hydroxytridecyl methyl sulfoxide, 3-hydroxy-4-dodecoxybutyl methyl sulfoxide.

7. Alkylated polyglycosides wherein the alkyl group is from about 8 to about 20 carbon atoms, preferably about 10 to about 18 carbon atoms and the degree of polymerization of the glycoside is from about 1 to about 3, preferably about 1.3 to about 2.0.

When dosing a mammal systemically, the quantity of antibacterial compound is from about 0.01 to about 50, desirably about 0.1 to about 10 and more desirably about 0.02 to about 5. All doses are on the basis of mg/kg (body weight)/day and can be provided one to four times per day to the patient.

Studies showing the antibacterial activity of these compound(s), particularly the drug resistant, methicillin resistant antibacterial activity, are present as shown below.

Evaluation of Several Phenolic Antimicrobial Agents Against Staphylococcus Aureus

Experimental Method:

Antimicrobial activity of several compounds was measured by determining the minimum inhibitory concentration (MIC). MIC is defined as the lowest concentration of an antimicrobial agent that will inhibit the growth of a microorganism and is usually expressed as ppm (μg/mL). MIC was determined by the Broth Dilution Method. To determine MIC a series of culture tubes was prepared, each tube containing the growth medium (Broth) with a decreasing concentration of the antimicrobial agent. The tubes were then inoculated with the test organism and incubated at 37°C. After incubation, tubes were visually examined for growth as indicated by turbidity. The lowest concentration that prevented visible growth is the MIC. MIC values for various compounds tested using Staphylococcus Aureus as the test organism are shown in Table 1.

TABLE I

MIC Results For Several Phenols Against Staphylococcus Aureus

Compound	MIC μg/mL
2-t-butyl-5-(4-t-butylphenyl)-phenol (DTBBP)	< 1.0
2-t-butyl-5-(4-t-butylcyclohexyl)-phenol	< 10.0
2-t-butyl-4-cyclohexylphenol	< 10.0
2-t-butyl-4-n-octylphenol	< 10.0

Evaluation of DTBBP Against Drug Resistant Strains of Staphylococcus Aureus

Experimental Method:

1. The following Staphylococcus Aureus isolates were tested:

TABLE 2

Isolate	Results
SA22	Resistant to methicillin, azithromycin, clarithromycin, erythromycin, ciprofloxacin, trovafloxacin)
SA76	Resistant to methicillin, azithromycin, clarithromycin, erythromycin, ciprofloxacin)
SA100	Resistant to methicillin only
SA6	Susceptible to all drugs
SA124	Susceptible
SA15	Susceptible

Grown overnight on blood plates. Colonies picked into 5 ml sterile water to a 0.5 MacFarland density. 50 µl into 5 ml M-H broth for a density of 10^6/mL.

2. 2-t-butyl-5-(4-t-butylphenyl)-phenol (DTBBP) was dissolved in ethanol to a concentration of 1000 µg/mL. Higher concentrations could not be tested due to the formation of precipitate in the broth when higher concentrations were attempted.

3. 100 µl of the 32 µg/ml solution added to column 12 of the multiwell plates, 50 µl M-H broth to each of the other columns. 50 µl removed from 12 to 11 for 1:1 dilution, continued to column 2. 50 µl removed from column 2 and discarded. Column 1 contained no drug. To control for the amount of ethanol added to each well, additional wells were set up as described above without DTBBP but with the same amount of ethanol as the test wells.

4. 50 μl bacteria added to each well going from column 1 to column 12. All isolates run in duplicate with and without DTBBP.

5. Addition of 50 μl bacteria to 50 μl drug dilutes both 1:1 for a final bacterial density of 5 X 10^5/ml and drug concentrations of:

0 μl
0.016 μl
0.032 μl
0.062 μl
0.125 μl
0.25 μl
0.5 μl
1 μl
2 μl
4μl
8μl
8μl

6. Incubated overnight at 37°C.

MIC Results For Antibiotic Resistant Staphyloccus Aureus Strains:

TABLE 3

Isolate	DTBBP MIC μg/mL (24 hr/48 hr)
SA22	2/2
SA76	2/4
SA100	4/4
SA6	2/4
SA15	2/4
SA124	2/4

Example of substituents of the compounds are shown below.

Examples of R_1 substituents of the active compounds are isobutyl, tert butyl, isoamyl, 2,3-dimethyl butyl, isoeicosyl, isododecyl, 2,2,4-trimethylpentyl, 2-ethylhexyl, 2-ethyl-5-methyldecyl, isooctadecyl, cyclobutyl, cyclohexyl, cycloheptyl, 3-cyclohexyloctyl, 3-methylcyclopentyl, 2,4-diethylcycloheptyl.

Examples of R_2 substituents of the active compounds are all of the R_1 group illustratively exemplified above as well as phenyl, benzyl, p-methyl phenyl, p-methyl benzyl, p-ethyl phenyl, p-isopropyl benzyl, p-t-butyl phenyl, p-1,1,3-trimethyl butyl benzyl, p-cyclohexyl phenyl, p-methyl cyclohexyl benzyl, p-4-t-butylcyclohexyl phenyl.

R_3 substituents are hydrogen, methyl, ethyl, propyl and isopropyl.

Preferred compounds of the invention are 2-t-butyl-5-(4-t-butylphenyl)-phenol (DTBBP), 2-t-butyl-5-(4-t-butylcyclohexyl)-phenol, 2-t-butyl-4-cyclohexylphenol, 2-t-butyl-3-octyloxyphenol, 2-t-butyl-4-n-octylphenol.

Examples of pharmaceutically acceptable salts of the phenolic compounds of this invention include alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium; strontium, amine salts such as ammonium, tetramethyl ammonium, triethanolamine, zinc; and the like.

Exemplary compositions of the invention are shown below.

EXAMPLE 1	
Hand Cleansing Composition	
Ingredient	Wt%
2-octyl-4-cyclohexylphenol	0.3
Propylene glycol	3.0
Lauramine oxide (30% active)	5.0
Hydroxyethyl cellulose	0.7
PH	5.5
Water	QS
TOTAL	100

EXAMPLE 2	
Dilutable Surface Cleaning Composition	
Ingredient	Wt%
2-t-butyl-4-(4-t-butylbenzyl)-phenol	14.0
N-methylpyrrolidone	9.7
N-octylpyrrolidone	14.1
Nonyl phenol ethoxylated alcohol with 9 EOs	14.0
Sodium dodecyl sulfate	14.0
Water	QS
TOTAL	100

Such a composition can be bucket dilutable to 10-200/l in water to make a stable cleaning solution.

EXAMPLE 3	
Hydrophilic Ointment (1% DTBBP)	
Ingredient	Wt%
2-t-butyl-5-(4-t-butylphenyl)-phenol	1.0
Methyl paraben	0.025
Propyl paraben	0.015
Sodium dodecyl sulfate	0.1
Propylene glycol	12.0
Stearyl alcohol	25.0
White petrolatum	25.0
Purified Water	QS (QS)
TOTAL	100

EXAMPLE 4	
Hydrophobic Ointment	
Ingredient	Wt%
2-t-butyl-5-(4-t-butylphenyl)-phenol	1
White wax	5
White petrolatum	QS
TOTAL	100

EXAMPLE 5	
Body Wash With Anionic Surfactant	
Ingredient	Wt%
Cocoamidyl Propyl Betaine	10
Sodium Laureth Sulfate 2EtO	9.3
Decyl Glucoside	2.3
Tetrasodium EDTA	0.08
Polyquaternium-7	0.2
Fragrance	1.0
2-Cyclohexyl-4-tert-Octyl Phenol	0.3
Salt (NaCl)	0.6
Citric Acid	0.6
D.I. Water	QS
TOTAL	100.0

5

EXAMPLE 6	
Aerosol For Hard Surface Cleansing	
Ingredient	Wt%
Cocoamidopropy. Betaine	3
Denatured Ethanol (94%)	1
Formalin	1
Fragrance	0.3
C_{9-11} Alcohol Ethoxylate (EO5-8)	1.6
Propylene Glycol-N-Butyl Ether	3
2-t-Butyl-4-Cyclohexyl Phenol	0.3
D.I. Water	QS
TOTAL	100

EXAMPLE 7	
Hand And Face Wash With Anionic Surfactant Polyquat System	
Ingredient	Wt%
C12-C14 alcohol-EO (1.0-2.0) Sulfate (Na salt)	8
Cocoamidopropyl betaine	10
Alkiyl Polyglycosine (APG-600)	1.2
Polyquaternium-7	0.2
2-t-butyl-4-(4-tbutylbenzyl)-phenol	0.3
Fragrance	0.4
Citric Acid	0.04
Dibromo-Dicyano Butane 10% in DPG	0.3
Water	QS
TOTAL	100.0

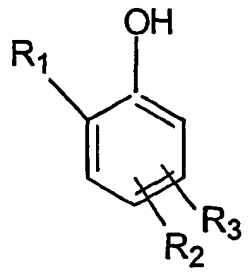
5

The pH of the compositions having the active compounds can range from about 5 to about 10, desirably about 6 to about 8.

Claims

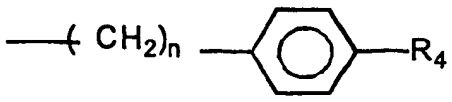
What is claimed is:

1. In accordance with the invention, there is a method for inhibiting drug resistant bacteria which comprises administering to a host or surface in need of said treatment a composition comprising an antibacterially effective amount against drug resistant bacteria of a compound or a mixture of compounds of the formula:



wherein R_1 is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and partially to fully alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;

R_2 is at the 4 or 5 position and is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;



wherein n is 0 or 1 and R_4 is selected from the group consisting of hydrogen, alkyl of one to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;

R_3 is selected from the group consisting of hydrogen and alkyl of three to eight carbon atoms with the provisio that when R_2 is at the 4 position then R_3 is at the 5 position and when R_2 is at the 5 position then R_3 is at the 4 position; and pharmaceutically acceptable salts thereof.

2. The method in accordance with claim 1 wherein the drug resistant bacteria are methicillin resistant.

3. The method in accordance with claim 2 wherein the drug resistant bacterial is staphylococcus aureus.

4. The method in accordance with claim 3 wherein the compound is selected from the group consisting of 2-t-butyl-5-(4-t-butylphenyl)-phenol (DTBBP), 2-t-butyl-5-(4-t-butylcyclohexyl)-phenol, 2-t-butyl-4-cyclohexylphenol, 2-t-butyl-3-octyloxyphenol, 2-t-butyl-4-n-octylphenol and mixtures thereof.

5. The method in accordance with claim 1 wherein the composition is administered topically to a host or a surface.

6. The method in accordance with claim 5 wherein there is a skin cleansing or surface cleansing amount of surfactant or mixture thereof in the composition.

7. The method in accordance with claim 6 wherein the surfactant or mixture thereof is at least 5 wt% of the formulation.

8. The method in accordance with claim 1 wherein the composition is systematically administered to a host in need of said treatment.

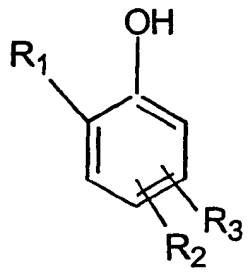
9. The method in accordance with claim 5 wherein the composition is administered to a host.

10. The method in accordance with claim 5 wherein the composition is administered to a surface.

11. A composition comprising:

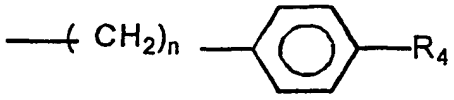
(a) at least about 5 wt% of a surfactant or mixture thereof; and

(b) an antibacterial effective amount of a compound of at least minimum effectiveness against methicillin drug resistant bacteria, said compound of the formula:



wherein R_1 is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;

R_2 is at the 4 or 5 position and is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms, and mono to tetrea alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;



wherein n is 0 or 1 and R4 is selected from the group consisting of hydrogen, alkyl of one to twenty carbon atoms, cycloalkyl of four to about eight carbon atoms, and mono to tetra alkyl substituted cycloalkyl of from four to about eight carbon atoms wherein alkyl is one to about four carbon atoms;

R3 is selected from the group consisting of hydrogen and alkyl of one to three carbon atoms with the proviso that when R2 is at the 4 position then R3 is at the 5 position and when R2 is at the 5 position then R3 is at the 4 position; and pharmaceutically acceptable salts thereof.

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Published:
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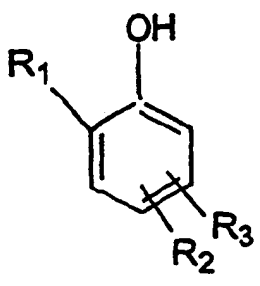
12 December 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/002098 A3

(54) Title: ANTIBACTERIAL METHOD AND COMPOSITION WITH PHENOLIC COMPOUNDS



(I)

(57) Abstract: A method for inhibiting drug resistant bacteria which comprises administering to a host or surface a compound of the formula (I): wherein R_1 is selected from the group consisting of branched alkyl or cycloalkyl; R_2 is at the 4 or 5 position and is selected from the group consisting of branched alkyl of four to about twenty carbon atoms, cycloalkyl of from four to about eight carbon atoms, mono cycloalkyl substituted alkyl of from four to about twelve carbon atoms where cycloalkyl is about four to about eight carbon atoms. R_3 is selected from the group consisting of hydrogen and alkyl of one to three carbon atoms with the proviso that when R_2 is at the 4 position then R_3 is at the 5 position and when R_2 is at the 5 position then R_3 is at the 4 position.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/US 01/20705

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/05 A61P33/00 A61L2/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, MEDLINE, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 912 274 A (SUBRAMANIAN MALATHY ET AL) 15 June 1999 (1999-06-15) the whole document ---	1-11
X	US 5 998 487 A (SHAPIRO STUART ET AL) 7 December 1999 (1999-12-07) abstract column 1, line 1 -column 3, line 32; claims 1-9; example 2; tables 1-5 ---	1-3,5-11
X	SHAPIRO, STUART ET AL: "Inhibition of oral bacteria by phenolic compounds. Part 1. QSAR analysis using molecular connectivity" QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS (1998), 17(4), 327-337 , XP008007715 the whole document ---	1-3,5-7, 9-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2002	27/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10800 A (COLGATE PALMOLIVE CO) 27 March 1997 (1997-03-27) abstract page 1, line 6 -page 8, line 34; claims 1-6,9-14; example 2	1-7,9-11
X	US 4 022 911 A (GOLDHAFT TEVIS M ET AL) 10 May 1977 (1977-05-10) abstract; example 1 column 1, line 1 -column 5, line 10	1-3,5-11
X	CHOI, MI-AE ET AL: "Identification and antibacterial activity of volatile flavor components of Cordyceps militaris" JOURNAL OF FOOD SCIENCE AND NUTRITION (1999), 4(1), 18-22 , XP001100085 abstract; tables 1-3 page 22, column 1, paragraph 3	1,3,5-11
X	EP 0 648 415 A (KURITA WATER IND LTD) 19 April 1995 (1995-04-19) abstract page 2, line 39 -page 3, line 20	11
A	US 3 832 459 A (BERKELEY B) 27 August 1974 (1974-08-27) the whole document	1-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,5-11 relate to a large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 01/20705

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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